Response to Rejection Under 35 U.S.C. § 112

Claims 8-14 and 21-34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner holds that "the claims are vague and indefinite as to what is meant regarding the metes and bounds of the phrase "randomly distributed"." The Examiner further points out that this "unclarity exists in independent claims 8, 13 and 14 and claims dependent therefrom directly or indirectly due to their dependence."

Without arguing with the propriety of the rejection, Applicants have amended the claims following the Examiner's suggestion. Claims 8, 13 and 14 have been amended to particularly point out that the population of microspheres comprising subpopulations of microspheres are randomly distributed on the surface comprising discrete sites, and that discrete sites have a single microsphere.

Therefore, Applicants respectfully submit that the amended claims are allowable under 35 U.S.C. § 112.

Response to Rejection Under 35 U.S.C. § 102

Claims 16-18 are rejected under 35 U.S.C. § 102(b) and (e) as being clearly anticipated by Ekins et al. (U.S. Patent No. 5,516,635).

As the Examiner is aware, "[i]t is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

Claims 16-18 are directed to a method of making a microsphere array comprising applying energy in the form of agitation to facilitate random association of particles onto discrete sites on a surface of a substrate.

In contrast, Ekins et al. teaches a binding assay process for an analyte using a capture binding agent with binding sites specific for the analyte and a developing binding material capable of binding with the bound analyte or with the binding sites on the capture binding agent either occupied by the bound analyte or the remaining unoccupied binding sites.

Specifically, the Examiner refers to Example 5 in Ekins et al. This example illustrates an ultra-sensitive sandwich two-step back titration TSH microspot immunoassay employing developing antibody conjugated to fluorescent microspheres. During the first step, anti-TSH capture antibody was spotted, i.e., at a known location, in the microtitre wells, column 13, line 29-31. During the second step, an aliquot of developing binding material antibody conjugated to fluorescent-dye containing microspheres was added to each well and shaken for 0.5 to 1 hour, column 13, line 44-49. Subsequently, the signal emitted from each antibody microspot was quantified, column 13, line 54-57. Therefore, the shaking, a form of agitation, applied in Ekins et al., was to promote specific interaction between the developing binding material antibody conjugated to fluorescent-dye containing microspheres and the microspots occupied by the anti-TSH capture antibody. A form of agitation that facilitates random distribution of microspheres within microtitre wells would clearly defeat the purpose of Example 5 in Ekins. Moreover, agitation that facilitates random distribution of microspheres is not taught anywhere in Ekins et al.

Accordingly, because Ekins fails to teach each element of claims 16-18, Ekins does not anticipate the method of claims 16-18. Applicants respectfully request the Examiner to withdraw this rejection.

Claims 8-18 and 21-34 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Walt et al. (U.S. Patent No. 6,023,540).

Again, as the Examiner is aware, "[i]t is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

Claims 8-18 and 21-34 are directed to a method of decoding an array comprising randomly distributed bioactive agents-labeled microspheres onto discrete sites on a patterned surface and addition of decoding binding ligands to said array to identify the location of said bioactive agents.

Walt et al. is directed to a microsphere-based analytic chemistry system in which microspheres carrying different chemical functionalities may be mixed together while the ability

is retained to identify the functionality on each bead using an optically interrogatable encoding scheme. Walt et al. elegantly present two synergistic inventions, which, when implemented together, yield an optical fiber sensor that supports large numbers of separate chemical functionalities and is easier to manufacture and use than previous methods of building on the sensor's end various chemical functionalities in a serial fashion. Nevertheless, Walt et al. relies on a system of optical signature encoding of the optical fiber sensor and is explicitly silent with respect to decoding binding ligands.

In contrast, claim 13 in this application specifically excludes the presence of an optical signature in the microspheres. Therefore, Walt et al. does not meet every element in claim 13.

Claims 8, 14 and 29 and their dependent claims are directed to methods of determining the presence of a target analyte in a sample comprising a step of adding a plurality of decoding binding ligands to identify a plurality of bioactive agents present in different subpopulations of microspheres. The element of this adding step is not anticipated by Walt et al., because the description of preferred embodiments in the patented invention is silent with respect to an additional step of adding decoding binding ligands to the system. Rather, it is directed to identification of optical signatures encoded in or on microspheres. Therefore, Walt et al. does not meet every element in claims 8, 14 and 29.

Accordingly, the claims at issue are allowable under 35 U.S.C. § 102.

Response to Rejection under 35 U.S.C. § 103

Claims 8-14, 21, and 23-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ekins et al. (U.S. Patent No. 5,516,635).

Ekins et al. teaches a binding assay process for an analyte using a capture binding agent with binding sites specific for the analyte and a developing binding material capable of binding with the bound analyte or with the binding sites on the capture binding agent either occupied by the bound analyte or the remaining unoccupied binding sites.

Specifically, Example 5 in Ekins et al. illustrates an ultra-sensitive sandwich two-step back titration TSH microspot immunoassay employing developing antibody conjugated to

fluorescent microspheres. During the first step, anti-TSH capture antibody was spotted, i.e., at a known location, in the microtitre wells, column 13, line 29-31. During the second step, an aliquot of developing binding material antibody conjugated to fluorescent-dye containing microspheres was added to each well and shaken for 0.5 to 1 hour, column 13, line 44-49. Subsequently, the signal emitted from each antibody microspot was quantified, column 13, line 54-57. Therefore, the fluorescence-labeled microspheres did not randomly distribute within each well, but rather specifically bound to anti-TSH capture antibody microspots.

The Examiner cites the Example 5 in Ekins et al. in column 13, and inferred from this example "a reasonable expectation of success that random distribution of these microspheres occurred within each well." The Examiner holds that "it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to perform the Ekins et al. assays with labeled microspheres in patterned microtitre plates with random distributions within each well thus resulting in the practice of the instant invention." Applicants respectfully traverse.

Applicants note that there are three requirements to establish a prima facie case of obviousness. These include that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." (MPEP § 2143).

Ekins et al. does not teach random distribution of labeled microspheres at discrete sites, including wells, at all. As outlined above, a random distribution of the fluorescence-labeled microspheres in the microtitre wells would completely defeat the purpose of the assay in the Example 5 in Ekins et al. cited by the Examiner.

Figures 3-5 in Ekins et al. further support Applicants' contention that Ekins et al. does not teach random distribution of microspheres in a well. In each of these figures, a microsphere M is shown to bind to a capture binding agent B immobilized by a microspot A. It would be obvious to a person of ordinary skill in the art that the interaction between capture binding agent and developing binding material conjugated to microspheres in Ekins et al. is of a specific nature.

Therefore, Ekins et al. does not provide motivation to employ a method of decoding array sensors formed by random association of labeled-microspheres onto discrete sites on a patterned surface.

In addition, Applicants submit that even assuming, arguendo, that there is motivation, Ekins et al. does not lead to the method of claims 8-14, 21 and 23-34. That is, the skilled artisan would not have a reasonable expectation of practicing the invention as claimed. Because the assays in Ekins et al. rely on a form of specific interaction between a developing binding material and a capture binding agent or an analyte, Ekins et al. does not provide a reasonable expectation of success of random distribution of microspheres at discrete sites, such as wells.

Finally, Applicants submit that Ekins et al. fails to teach or suggest all the claim limitations. Because this application employs a method of randomly distributing microspheres onto discrete sites on a patterned surface, Ekins et al. does not teach or suggest all the claim limitations in this application.

Accordingly, Applicants submit that a prima facie case of obviousness has not been made. Applicants respectfully request the Examiner to withdraw the rejection.

Response to Objection to Claims 19 and 20

Claims 19 and 20 are objected to as being dependent upon a rejected base claim, which is claim 16.

Applicants respectfully submit that, because claim 16 in the amended form is allowable, this objection should be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

For the Examiner's convenience, a clean copy of the currently pending claims is attached hereto.

Applicants submit that the claims as amended are in form for immediate allowance and the Examiner is respectfully requested to early notification to that effect.

The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues may be resolved in that manner.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the claims:

8. (Amended) A method of decoding an array composition comprising

a) providing an array composition comprising:

i) a substrate with a patterned surface comprising discrete sites; and

ii) a population of microspheres comprising at least a first and a second subpopulation, wherein each subpopulation comprises a bioactive agent;

wherein said population of microspheres is [are] randomly distributed on said surface such that any discrete site has at most a single associated microsphere;

b) adding a plurality of decoding binding ligands to said array composition to identify the location of at least a plurality of the bioactive agents.

13. (Amended) A method of determining the presence of a target analyte in a sample comprising:

a) contacting said sample with a composition comprising:

i) a substrate with a patterned surface comprising discrete sites; and

ii) a population of microspheres comprising at least a first and a second subpopulation each comprising a bioactive agent and [do] not comprising [comprise] an optical signature;

wherein said population of microspheres is [are] randomly distributed on said surface such that any discrete site has at most a single associated microsphere [said discrete sites contain microspheres]; and

b) determining the presence or absence of said target analyte.

14. (Amended) A method of determining the presence of a target analyte in a sample comprising:

a) contacting said sample with a composition comprising:

i) a substrate with a surface comprising discrete sites; and

ii) a population of microspheres comprising at least a first and a second

subpopulation each comprising:

1) a bioactive agent; and

2) an identifier binding ligand that will bind a decoder binding ligand such that the identification of the bioactive agent can be elucidated;

wherein said population of microspheres is [are] randomly distributed on said surface such that any discrete site has at most a single associated microsphere [said discrete sites contain microspheres]; and

b) determining the presence or absence of said target analyte.

16. (Amended) A method of making a microsphere array comprising:

a) contacting a substrate with a surface comprising discrete sites with a solution comprising a population of particles; and

b) applying energy to said substrate or said solution, or both, such that at least a subpopulation of said particles randomly associates onto sites.

20. (Amended) A method according to claim 16 [19], wherein said substrate is a fiber optic bundle.

New claim:

35. A method according to claim 8, wherein said bioactive agents are nucleic acids.